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ARE ESTROGENS ALONE REALLY SAFE FOR BREAST IN MENOPAUSAL THERAPY?

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The results from of the Women health initiative trial in hysterectomized women had given unexpected results concerning breast cancer (BC) risk. Women randomized between conjugated estrogen treatment alone or placebo displayed a lower risk of BC in the active group. This is at odd comparing these results with those from observational studies which, in their great majority, showed an increase relative risk of BC. The range of the risk appeared however at a lower range than with the menopausal combined therapy (MHT). Furthermore the increase began significant after longer term than with MHT. A protective effect of estrogens for breast cancer is quite contradictory to what the preclinical data say. The estrogen/hormone dependent character of BC is fully acknowledge. A large amount of preclinical studies have shown the proliferative and antiapoptotic effects of estradiol in hormonedependent breast cancer cells. Antiestrogen therapy can not only decrease the risk of recurrence or bilateral BC but also are effective in prevention of BC, illustrating the importance of estrogen signaling in the progression of BC. However, estradiol positive BC are usually of a better prognosis than ER negative BC, presence of ER interpreted as a marker of better differentiation. One of the first explanation for the WHI results could be that conjugated estrogens were used instead of estradiol as those compounds contain hundreds of estrogenic and antiestrogenic derivatives with unpredictable effects on the breast. Another possibility could be that obesity was highly prevalent in this population and that estrogen treatment decreased the insulin resistance with a beneficial effect on BC risk. The third interpretation is that estrogen acting on breast devoid of estrogen for years as the population of the WHI was far from menopause, could display a proapoptotic effect on BC cells. In addition the dose of estrogen administered could also matter since very high doses were shown to improve the treatment of BC. Available evidence for the impact of estradiol on normal and breast cancer using data from epidemiology to biology will be discussed.

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